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Normative Database of Peripapillary Vessel Density Measured by Optical Coherence Tomography Angiography and Correlation Study

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ABSTRACT

Purpose: To provide a normative data set of swept-source optical coherence tomography angiography (SS-OCTA) peripapillary vessel density (VD) measurements and assess correlations with age, gender, disc area and axial length (AL).

Material and Methods: This was an observational cross-sectional study conducted on 346 right eyes of healthy subjects. Peripapillary SS-OCTA VD measurements were obtained in the retinal superficial capillary plexus (SCP), deep capillary plexus (DCP), and choriocapillaris (CC) in all four quadrants using the Triton device (Topcon, Nagoya, Japan). AL measurements were made by optical biometry.

Results: Mean participant age was 37.7 ± 19.8 years (range 5–83), AL was 23.9 ± 1.3 mm (21–27), and 59% were women. Mean VDs for all quadrants were $57.2 \pm 5.7\%$ for SCP ($52.4 \pm 4.0\%$ – $62.1 \pm 4.2\%$), $46.3 \pm 6.5\%$ for DCP ($41.9 \pm 5.8\%$ – $49.7 \pm 4.8\%$) and $60.8 \pm 7.4\%$ for CC ($53.4 \pm 5.8\%$ – $65.7 \pm 5.5\%$). Negative correlation was detected between SCP VD and age ($R = -0.264$; $P < .001$), while correlation between DCP densities and age was positive ($R = 0.202$; $P = .002$). No associations were detected between peripapillary VD and gender ($P \geq 0.087$) and negative correlation was found with AL and disc area only in the CC ($P \leq 0.004$). In a subgroup analysis of 33 individuals, we noted no differences in VD between fellow eyes ($P \geq 0.139$).

Conclusion: Peripapillary VD showed wide individual variation when measured with the Triton SS-OCTA in the different retinal plexuses and CC. While correlations were observed with age, no relationships emerged with gender and only CC showed negative correlation with AL and disc area.

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Introduction

Vascular dysfunction plays a key role in the pathogenesis of glaucoma, as many studies have shown.^{1–3} However, knowledge about the relationship between abnormal ocular perfusion and glaucoma is still scarce mainly because of limitations in determining optic nerve head (ONH) blood flow.^{4,5}

By optical coherence tomography angiography (OCTA), a recently introduced technique, the microcapillaries of the ONH and peripapillary region can be easily visualized without the need for dye injection.^{4–10} This technique based on comparing B-scans via OCTA algorithms is able to detect red blood cell motions and can therefore be used to visualize microvascular flow.

Among the quantitative metrics used to describe the state of the ONH and peripapillary vessels offered by current OCTA devices, one of the most popular is vessel density (VD).^{8,9,11–13} So far, OCTA has proved useful to evaluate ONH VD in patients with suspected or confirmed glaucoma.⁵ The clinical relevance of taking peripapillary VD measurements is that the amount of VD reduction produced seems related to the extent of functional loss in glaucoma.

Using this technique, Jia et al. were the first to describe a reduction in ONH and peripapillary VD in pre-perimetric and primary open-angle glaucoma (POAG) compared to controls.⁴ Interestingly, in patients with suspected or confirmed glaucoma, Triolo et al. observed evident structural damage in both peripapillary and macular vessel networks.¹⁴ Moreover, OCTA has been successfully used to distinguish between healthy subjects, patients with ocular hypertension, glaucoma suspects, and patients with POAG.^{14,15} Diminished VD has also been reported in other types of glaucoma such as normal-tension,^{6,7} primary angle-closure^{16,17} or exfoliation.¹⁸ Several studies have also detected strong correlation between OCTA parameters and the thickness of the retinal nerve fiber layer (RNFL)^{5,19} or ganglion cell complex.²⁰ Further, peripapillary VD has been correlated moderately to highly with visual field (VF) parameters.^{4,10,21}

As this technology is relatively new, there are still few large normative OCTA databases and little is also known about the influence of or correlation between different parameters and peripapillary or ONH VD.^{8,11} Thus, there is a need for

normative VD data before OCTA technology can be routinely used in clinical practice and trials to guide the diagnosis and management of glaucoma. We will then be able to compare these reference data with measurements made in the different types of glaucoma for an effective diagnosis and to detect glaucoma progression^{4-7,22,23} ideally in early disease stages but also in advanced stage disease.^{13,15}

With this purpose in mind, the present study was designed to provide normative peripapillary data of the retinal plexus and choriocapillaris (CC) obtained through SS-OCTA in a large population of healthy individuals. Once these data were compiled, we examined correlations between VD measurements and the factors gender, age, disc area and axial length (AL).

Methods

The participants of this cross-sectional study were 346 healthy volunteers. Patients attending the Centro Internacional de Oftalmología Avanzada (Madrid, Spain) for a routine eye examination were enrolled over the period February 1, 2018 to January 10, 2019. Once it was ensured that all the established inclusion criteria were met, candidates were invited to participate. After explaining the nature of the study protocol and its objectives, participants gave their written consent to participate. The study protocol was in line with the Declaration of Helsinki and received Institutional Review Board approval.

For enrollment it was required that subjects be healthy Caucasian (white race) with an intraocular pressure equal to or under 21 mm Hg in both eyes, and an AL of 21 to 27 mm (mean AL among our patients is 24 mm). Subjects were excluded if they had a self-proclaimed systemic or eye disease (or one found in the ophthalmological examination), ocular media opacification, had undergone previous eye surgery or were taking any systemic medication. Subjects were also excluded if their corresponding images had a motion artifact consisting of a discontinuous vessel pattern or discontinuous disc boundary. The presence of strabismus and ocular torsion were ruled out in the examination and in the fundus photograph. Measurements for the right eye only were analyzed.

Participants were subjected to a full ophthalmologic examination and OCTA on the same day. The parameters recorded were visual acuity and refraction, and slit-lamp biomicroscopy and posterior segment ophthalmoscopy findings. Also recorded were age, gender and AL (IOL master 500; Carl Zeiss Jena, Germany). To assess inter-eye differences, data for the left eye were also considered in the first 33 participants examined.

For the VD measurements, we used the Triton OCTA device (Topcon, Tokyo, Japan). The instrument's working conditions were: central wavelength 1,050 nm, axial resolution 8 μ m, transverse resolution 20 μ m, and scan speed 100,000 A-scans/s. All OCTA measurements were made after pupil dilation (Colircusi tropicamide 10 mg/ml, Alcon Laboratories, Inc., Fort Worth, TX) by a well-trained examiner (HS) with the subject sitting and looking at a fixed point. Only images of sufficient quality (signal strength intensity (SSI) >40) were accepted.

The algorithm used by the Triton device was OCTA-ratio analysis (OCTARA, full-spectrum ratio-based amplitude ratio analysis) keeping the full-spectrum intact and preserving axial resolution. Vessel density was defined as the percentage of vessel area showing blood flow out of the total area measured and determined through adaptive thresholding binarization. Selecting the mode "angio macula", a 6 $\times$ 6 mm scan was centered manually at the ONH and VD measurements made in the peripapillary quadrants: superior, inferior, nasal and temporal. These quadrants were identified using an ETDRS grid overlay comprising the two inner rings. Vessel densities were obtained after applying the device's projections removal algorithm to the deep capillary plexus (DCP) and CC images. Images were first checked for good segmentation and the disc area was measured.

Peripapillary VD measurements were automatically segmented by the software algorithm (version 2014.2.0.65) for the superficial capillary plexus (SCP), DCP and CC. According to these default settings, the SCP network runs from 2.6 μ m below the internal limiting membrane to 15.6 μ m below the inner plexiform layer (IPL); DCP runs from 15.6 μ m to 70.2 μ m below the IPL; and CC runs from the Bruch membrane to 10.4 μ m beneath it (Figure 1). This determined that the nerve fiber layer plexus (NFLP; traditionally known as the radial peripapillary capillaries) and ganglion cell layer plexus (GCLP) were included in the SCP by the software employed.

Statistical analysis

For the statistical treatment of data, we used the software package SPSS® (Statistical Package for Social Sciences, v18.0; SPSS Inc., Chicago, IL, USA). Data are provided as the mean and standard deviation for quantitative variables, and frequency distributions for qualitative variables. To establish reference VD values for the different plexuses, percentile distributions (P5 and P95) were estimated. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. We used the Pearson's correlation procedure to assess correlations between peripapillary VD and the remaining variables and between data for right and left eyes in the subgroup examined. SCP versus DCP VD and right versus left eye measurements were compared using a paired t-test. We also conducted a multivariate stepwise linear regression analysis to identify the main factors determining a greater or lesser peripapillary VD. Significance was set at $p < .05$.

Results

Mean participant age was 37.7 ± 19.8 years (range 5–83); 59% were women. Mean AL was 23.9 ± 1.3 mm (21–27), mean optic disc area was 2.09 ± 0.38 mm² (1.41–3.27) and scan quality was 63.0 ± 6.8 SSI (41–77). All variables studied were normally distributed.

Mean peripapillary VD was $57.2 \pm 5.7\%$ for SCP, $46.3 \pm 6.5\%$ for DCP and $60.8 \pm 7.4\%$ for CC. Mean VDs for SCP were significantly higher than for DCP ($P < .001$ for all quadrants) (Table 1).

Figure 1. Example of a 6 × 6 mm optic nerve head (ONH) vessel density map showing measurements taken across the peripapillary quadrants segmented into the superficial capillary plexus (SCP), deep capillary plexus (DCP) and choriocapillaris (CC) layer.

Table 1. Swept source optical coherence tomography angiography (SS-OCTA) peripapillary vessel densities measured in the different retinal plexuses and choriocapillaris expressed as percentages (mean ± standard deviation and range) and percentile distributions (P5 and P95).

Peripapillary VD	SCP ^a	DCP ^b	CC ^c
Whole	57.2 ± 5.7 (37.6– 74.6) P5 – P95: 48.1– 65.9	46.3 ± 6.5 (26.7– 70.5) P5 – P95: 35.6– 56.8	60.8 ± 7.4 (29.9– 79.9) P5 – P95: 48.4– 72.2
Superior	59.9 ± 4.3 (42.7– 74.6) P5 – P95: 52.7– 66.0	41.9 ± 5.8 (26.7– 65.3) P5 – P95: 33.3– 51.2	58.8 ± 5.3 (35.9– 71.1) P5 – P95: 49.1– 66.9
Inferior	62.1 ± 4.2 (38.6– 71.5) P5 – P95: 54.9– 68.2	45.3 ± 7.1 (28.6– 66.7) P5 – P95: 34.3– 58.2	53.4 ± 5.8 (30.2– 72.6) P5 – P95: 44.0– 62.0
Temporal	52.4 ± 4.0 (37.6– 63.6) P5 – P95: 45.3– 58.7	48.2 ± 5.2 (32.1– 70.5) P5 – P95: 40.6– 56.8	65.4 ± 4.8 (52.7– 79.9) P5 – P95: 57.8– 73.2
Nasal	54.2 ± 3.7 (42.6– 69.0) P5 – P95: 48.1– 59.9	49.7 ± 4.8 (36.5– 68.5) P5 – P95: 41.5– 57.7	65.7 ± 5.5 (29.9– 76.0) P5 – P95: 55.8– 73.8

^aSCP = superficial capillary plexus; ^bDCP = deep capillary plexus; ^cCC = choriocapillaris.

In the SCP, vertical peripapillary VDs were higher than horizontal measurements ($P < .001$). For CC, higher mean peripapillary VDs were observed in the horizontal (nasal $65.7 \pm 5.5\%$ and temporal $65.4 \pm 4.8\%$) than vertical quadrants (superior $58.8 \pm 5.6\%$ and inferior $53.6 \pm 5.9\%$; $P < .001$).

When comparing vessel densities across the different peripapillary plexuses (Table 2), correlation was observed between SCP and DCP (from $R = 0.169$ to 0.516 ; $p \leq 0.002$). However, DCP and CC showed weak negative correlation between the inferior and nasal quadrants ($R = -0.256$ and $R = -0.162$; $P < .001$). In the subgroup of 33 subjects, no differences were observed in VD between fellow eyes ($P \geq 0.139$).

We detected negative correlation between peripapillary SCP VD and age (from $R = -0.264$ to $R = -0.166$ for all

Table 2. Correlations between peripapillary vessel density (VD) measured in the different vascular plexuses (superficial capillary plexus = SCP; deep capillary plexus = DCP; and choriocapillaris = CC).

Peripapillary VD	Parameter	Correlation (p value)
Superior	SCP – DCP	0.239 ($P < .001$)
	SCP – CC	0.076 ($P = .162$)
	DCP – CC	-0.052 ($P = .340$)
Inferior	SCP – DCP	0.169 ($P = .002$)
	SCP – CC	0.021 ($P = .695$)
	DCP – CC	-0.256 ($P < .001$)
Temporal	SCP – DCP	0.385 ($P < .001$)
	SCP – CC	0.387 ($P < .001$)
	DCP – CC	0.055 ($P = .309$)
Nasal	SCP – DCP	0.516 ($P < .001$)
	SCP – CC	-0.050 ($P = .360$)
	DCP – CC	-0.162 ($P = .003$)

quadrants; $P \leq 0.002$), and positive correlation between DCP vessel densities and age in the vertical quadrants ($R = 0.202$ and 0.240 for the superior and inferior quadrants respectively; $P \leq 0.002$). (Table 3 and Figure 2). The association between age and VD was also analyzed in the subgroup of patients ≤ 18 years of age ($n = 60$) but no significant correlation was found (SCP $R = -0.123$, $P = .329$; DCP $R = 0.053$, $P = .673$; CC $R = -0.025$, $P = .841$; Spearman test).

For disc area, we detected no significant correlation with SCP VD, but weak positive association with DCP VD was found ($R \leq 0.236$). On the contrary, negative correlation was noted between CC VD and disc area ($R = -0.349$ to -0.273 ; $P \leq 0.001$).

In our multivariate regression analysis, age remained as a determinant of peripapillary VD ($P < .001$) for all plexuses. However, no association was found between peripapillary VD and gender ($P \geq 0.087$) regardless of the network examined. Only CC VD showed correlation with AL ($P = .004$). Disc area persisted as a significant determinant of DCP- and CC VD (Table 4).

Discussion

To confidently employ OCTA technology for quantitative metrics in clinical research and practice, normative peripapillary VD data are needed. Once we acquire these reference data, we will be able to

Table 3. Correlation between peripapillary vessel density (VD) and age or disc area (N = 346). Correlation between peripapillary VD in the right and fellow eye is also shown (data recorded in 33 subjects).

Peripapillary VD	Quadrant	Age (years)	Disc area (mm ²)	Fellow eye (N = 33)	Fellow eye paired t test (N = 33)
SCP ^a	Superior	R = -0.264 P < .001	R = -0.005 P = .931	R = -0.100	P = .572
	Inferior	R = -0.247 P < .001	R = -0.064 P = .248	R = 0.084	P = .637
	Temporal	R = -0.189 P < .001	R = 0.147 P = .088	R = -0.242	P = .167
	Nasal	R = -0.166 P = .002	R = 0.073 P = .188	R = -0.218	P = .215
DCP ^b	Superior	R = 0.202 P = .002	R = 0.236 P < .001	R = 0.075	P = .673
	Inferior	R = 0.240 P = .000	R = 0.186 P < .001	R = 0.052	P = .771
	Temporal	R = -0.057 P = .292	R = -0.003 P = .157	R = -0.356	P = .139
	Nasal	R = -0.068 P = .213	R = 0.178 P < .001	R = -0.019	P = .916
CC ^c	Superior	R = 0.040 P = .464	R = -0.325 P < .001	R = -0.097	P = .584
	Inferior	R = -0.126 P = .060	R = -0.341 P < .001	R = 0.005	P = .998
	Temporal	R = -0.352 P = .052	R = -0.349 P < .001	R = -0.056	P = .752
	Nasal	R = -0.066 P = .226	R = -0.273 P < .001	R = 0.137	P = .438

^aSCP = superficial capillary plexus; ^bDCP = deep capillary plexus; ^cCC = choriocapillaris.

compare them with VD measurements obtained in the different types of glaucoma and optic nerve diseases to detect different abnormalities, ideally in early disease stages.^{4-7,13,15,22,23}

In the present study, we used an SS-OCTA device equipped with automatic software to quantify peripapillary VD not only in the retinal SCP, but also in the DCP and in the CC, obtaining a mean VD of $57.2 \pm 5.7\%$, $46.3 \pm 6.5\%$ and $60.8 \pm 7.4\%$ respectively. In the SCP, VD was greater in the vertical (superior $59.9 \pm 4.3\%$, inferior $62.1 \pm 4.2\%$) than horizontal quadrants (temporal $52.4 \pm 4.0\%$, nasal $54.2 \pm 3.7\%$), probably because of the presence of the larger retinal vessels.

In an interesting study, Bazvand et al. generated a normal quantitative database of peripapillary VD measurements made

Table 4. Multivariate regression analysis of factors determining a greater or lesser peripapillary vessel density (VD).

Dependent variable: peripapillary SCP ^a VD	Unstandardized beta	p
Constant	60.447	.000
Age (years)	-0.064	<.001*
Gender (male)	-0.035	.954
Axial length (mm)	-0.134	.583
Scan quality (signal strength intensity)	0.086	.041*
Disc area (mm ²)	0.000	1.000
Dependent variable: peripapillary DCP ^b VD	Unstandardized beta	p
Constant	33.611	.001
Age (years)	0.078	<.001*
Gender (male)	-0.986	.234
Axial length (mm)	-0.102	.760
Scan quality (signal strength intensity)	0.044	.442
Disc area (mm ²)	2.874	.006*
Dependent variable: peripapillary CC ^c VD	Unstandardized beta	p
Constant	43.833	.000
Age (years)	-0.061	<.001*
Gender (male)	-0.347	.648
Axial length (mm)	-0.862	.004*
Scan quality (signal strength intensity)	-0.029	.584
Disc area (mm ²)	-5.576	<.001*

^aSCP = superficial capillary plexus; ^bDCP = deep capillary plexus; ^cCC = choriocapillaris.

using the RTVue XR Avanti (Optovue, Fremont, CA, USA) in 79 eyes; the mean VD reported was $60.5 \pm 2.4\%$.¹¹ In another study in 181 eyes of 107 subjects, using the same device (RTVue XR Avanti), Rao et al. detected a median peripapillary VD of 62.7% .⁸ Also in accordance with our findings for the SCP ($57.2 \pm 4.0\%$), Akagi et al. observed a peripapillary VD in 21 normal eyes of $55.2 \pm 3.4\%$,²¹ while Falavarjani et al. obtained a mean of $60.1 \pm 2.8\%$ in 58 healthy individuals.²⁴ In the study of Bazvand et al., the highest VD was recorded in the inferotemporal subfield ($62.5 \pm 3.8\%$).¹¹ Similarly, Rao et al. also recorded higher densities for the inferotemporal and superotemporal subfields (both 66.8%).⁸ In our study, the highest VD for the SCP was recorded in the inferior quadrant ($62.1 \pm 4.3\%$).

Few authors have provided data for peripapillary CC VD. Here, we obtained an overall mean of $60.8 \pm 5.3\%$ across the different quadrants, and the higher VDs were observed in the nasal and temporal peripapillary quadrants (both $\geq 65\%$). Similar values were reported by Wang et al. for 110 healthy

Figure 2. Correlations between peripapillary vessel density (VD) and age in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) indicating that, with age, SCP VD decreases and DCP VD increases.

participants (mean peripapillary CC VD $64.9 \pm 2.7\%$).²⁵ Contrasting with our findings, Yip et al. did not detect in 55 healthy participants using the RTVue XR Avanti a higher choroidal peripapillary VD in the horizontal than vertical quadrants (nasal and temporal: 0.236 ± 0.094 and 0.192 ± 0.101 respectively, versus inferior and superior: 0.229 ± 0.084 and 0.260 ± 0.101 respectively).²⁶ Future studies of CC peripapillary vasculature analyzing different sectors are needed to determine why CC showed higher VDs in the horizontal sectors. As an explanation, it could be that as the ciliary arteries run on each horizontal side of the optic nerve, when they divide, a greater number of short posterior ciliary arteries enter the horizontal sectors. Another possibility would be that small branches of the two long posterior ciliary arteries penetrate the sclera on both sides of the optic nerve, in the horizontal meridian, despite their main function being to nourish the choroid anteriorly.

We found no significant difference in peripapillary VD measurements between both eyes in a subgroup of individuals ($N = 33$; $P \geq 0.139$). Despite this, no correlation with the fellow eye was observed in any of the plexuses or quadrants examined ($R \leq 0.137$). Hou et al. observed 1.7% inter-eye peripapillary VD asymmetry in 55 healthy subjects and greater asymmetry at 2.2% in glaucoma patients ($P = .026$).²⁷

When we examined the impacts of different parameters on peripapillary VD, correlation with age was negative in SCP and positive in DCP. In a recent review of determining factors for VD, Brucher et al. concluded that age is a strong determinant of retinal VD, and that the VD of the superficial vasculature diminishes with age.²⁸ On the contrary, Bazvand et al. reported no significant differences in superficial peripapillary VD across different age groups ($N = 79$; range 12 to 67 years).¹¹ However, they admitted that they anticipated some VD changes, albeit mild, during ageing but that their small sample size likely precluded detecting these changes.¹¹ Interestingly in a study by Falavarjani et al. including 58 participants, similar positive correlation (as in our study in DCP) was observed between age and peripapillary ONH VD ($R = 0.277$; $P = .035$) assessed in face images.²⁴ Zheng et al. showed that in normal aging, flow deficits in the CC increased with age.²⁹ Interestingly, Orlov et al. described by fundus photography that three main traits (tortuosity, vessel bifurcation number, and vessel end-point number) showed significant changes with age.³⁰ Further studies are therefore needed to clarify the effects of age in the different plexuses.

We noted no gender differences in peripapillary VD in any of the plexuses or quadrants studied. Consistent with our results, Mansoori et al. found that gender had no effect on peripapillary VD ($P = .7$).¹⁹ In contrast, Bazvand et al. reported higher temporal and inferotemporal peripapillary VDs in women than men.¹¹ Rao et al. also reported greater peripapillary VD in female subjects in the nasal and inferotemporal quadrants.⁸ However, as forewarned by these authors, these higher VDs in females require validation in future studies.

No correlation was found here between AL and retinal VD measured in the peripapillary region, as reported by Wen et al. for superficial VD measurements made using the same

device as in our study in 75 healthy participants with a mean AL of 24.9 ± 1.3 mm (21.8–28.8) ($P = .904$).³¹ However, we found negative correlation between CC VD and AL. This has been shown in some studies.²⁸ We should highlight the study of Mastropasqua et al., who claimed that the total signal void area was significantly greater in myopic eyes than control eyes, and observed that the peripapillary region exhibited the greatest total signal void area ($p < .001$ vs macular region and peripheral retinal region).³²

We found a significant correlation between disc area and CC VD in our multivariate analysis, but not for the SCP. Similarly, Falavarjani et al. were unable to correlate peripapillary retinal VD with disc area in normal eyes ($R = 0.204$; $P = .125$).²⁴ However, the different device employed should be considered, as they used an RTVue XR Avanti device with two concentric circles with 1.5 and 3.4 mm diameter centered on the disc, and the Triton uses an ETDRS grid with 1 and 3 mm respectively for the papillary and peripapillary subfields respectively.

According to the findings of Werner et al., OCTA may be particularly appropriate in very early or late-stage disease, when standard functional or structural diagnostic tests fail to offer useful data.^{4,5,10,14,15} Werner and Shen mentioned that a preceding structural and functional decline does not necessarily mean causation but that this may reflect the metabolic changes of “sick” retinal ganglion cells.⁵ In contrast, in more advanced glaucoma, RNFL measurements reach a plateau limiting the utility of detecting changes, and progression can be assessed only via VF assessment. Fortunately, peripapillary VD seems to have less of a floor effect than RNFL thickness.^{5,33}

It should be highlighted that, as stated by many authors, absolute peripapillary VD values calculated with different algorithms are not directly interchangeable, as the dimensions of the area explored and the exact depth at which VD is assessed differ between instruments.^{5,9} This means that studies adopting VD as an outcome measure should not rely on external normative databases.⁹ Nonetheless, even with this lack of standardization, OCTA studies have provided important evidence of microvascular compromise in glaucoma.^{6,7,14–18,22,23} Hence, comparisons of measurements across OCTA devices and techniques should be considered with caution, and the same algorithm should be used for longitudinal monitoring of VD. Besides, differences between healthy and diseased eyes can be appreciated with different discriminatory abilities as a function of the plexus analyzed.^{7,9,33,34} In this regard, observations by Shin et al. indicate that although both SCP and DCP are sparser in glaucomatous eyes, only SCP VD shows comparable performance to RNFL thickness for a diagnosis of glaucoma, as these authors found that deep layer measurements were affected by AL and showed no relationship with glaucoma severity.⁷ Further, Liu et al. argue that the NFLP slab shows the best diagnostic accuracy for visualizing focal peripapillary perfusion defects, while the superficial vascular complex slab (SVC includes NFLP and GCLP) offers the best correlation with visual field. It is, therefore, possible that blood flow parameters are a better surrogate for function and better metric for monitoring glaucoma progression.³³

Our study has several limitations. For peripapillary measurements, the examiner has to manually locate the measurement zone at the optic disk. Also, the segmented peripapillary analysis offered by the software does not separately identify NFLP and GCLP, and these were here measured together in the SCP. The software provided with OCTA devices should include a more detailed analysis of the peripapillary subfields, for example offering results for 6 or 12 sectors.

There is also great interindividual variability in optic disc configurations which could affect structural peripapillary measurements. However, inter-individual variability in the shape and size of the ONH affects peripapillary less than papillary VD quantification, so peripapillary measurements appear to offer more useful diagnostic information and have become the focus of most research in this area.⁵ The software employed here included the larger vessels in the density measurements. However, Liu et al. showed that capillary density (CD) excluding larger vessels offered slightly better diagnostic accuracy than VD including larger vessels (area under the receiver operating characteristic curve NFLP-CD = 0.947 versus NFLP-VD = 0.934; SVC-CD 0.942 versus SVC-VD 0.919).³³ The authors claimed that both (CD and VD) showed excellent performance, and currently both parameters are considered to offer similar information. Ideally, it should be possible to remove the larger vessel in the analysis when studying the ONH VD.

In addition, a general limitation of VD quantification in OCTA devices is the projection artifact of the superficial layers over the deeper ones, which may affect the accuracy of measurements. Liu et al. developed a projection-resolved OCTA algorithm to effectively remove the projection artifact and provide clean angiograms of deeper vascular plexuses in the peripapillary area.³³ This research group showed that SVC is the best slab to detect glaucomatous changes in the macular region.³⁵ As previously described by Spaide et al., the problem of the slab based approach is that segmentation is needed and this segmentation may introduce errors.³⁶ A further limitation was the inclusion of only Caucasian subjects, limiting the external applicability of results. Finally, several factors (e.g., motion artifacts, measurement and analysis methods, image quality, lack of fovea-disc axis correction, the device threshold for the detection of blood vessels or systemic factors such as blood pressure, diabetes or unknown diseases) may modify VD and affect the accuracy and repeatability of VD measurements.^{37–39} Recently, using the Triton device, we reported the moderate reproducibility of these measurements, as have others employing different OCTA devices.^{40,41} In our previous study, peripapillary VD measurements in the same setting showed an intraobserver ICC ≥ 0.499 for all subfields and plexuses, with an interobserver ICC ≥ 0.620 .⁴⁰ The highest ICC recorded were for intraobserver reproducibility in the SCP (0.853) and CC (0.828). Interobserver agreement values were 0.870 for SCP and 0.868 for CC. The CV of the peripapillary measurements ranged from 4.8% to 16.4%. Overall, VD reproducibility coefficients were higher for the ONH (ICC ≥ 0.499) than macula (ICC ≥ 0.268). Accordingly, these variation sources need to be minimized to ensure reliability between exams.

Our study offers the largest and most complete SS-OCTA normative database using the Triton device of peripapillary VD

for the different retinal plexuses and the CC, as useful reference ranges to interpret VD measurements. It also assesses the impacts of different factors in a large healthy Caucasian population, which will be useful for interpreting OCTA metrics and identifying and characterizing pathological changes in these structures. This large dataset of peripapillary VD measurements revealed wide individual variation and correlations with age. No associations emerged with gender, and only in the CC, was VD negatively correlated with AL and disc area.

Disclosure statement

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